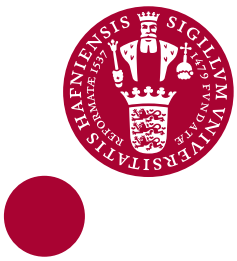

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Effect of diabetes duration on the relationship between glycaemic control and risk of death in older adults with type 2 diabetes

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Abstract

Aim: To investigate the effect of diabetes duration on glycaemic control, measured using mean glycated haemoglobin (HbA1c) level, and mortality risk within different age, sex and clinically relevant, comorbidity-defined subgroups in an elderly population with type 2 diabetes (T2D).

Methods: We studied older (≥65 years) primary care patients with T2D, who had three successive annual measurements of HbA1c taken between 2005 and 2013. The primary exposure was the mean of all three HbA1c measurements. Follow-up began on the date of the third measurement. Individual mean HbA1c levels were categorized into clinically relevant groups (<6.5% [<48 mmol/mol]; 6.5%-6.9% [48-52 mmol/mol]; 7%-7.9% [53-63 mmol/mol]; 8%-8.9% [64-74 mmol/mol]; and ≥9% [≥75 mmol/mol]). We used multiple Cox regression to study the effect of glycaemic control on the hazard of all-cause mortality, adjusted for age, sex, use of concomitant medication, and age- and disease-related comorbidities.

Results: A total of 9734 individuals were included. During a median (interquartile range) follow-up of 7.3 (4.6-8.7) years, 3320 individuals died. We found that the effect of mean HbA1c on all-cause mortality depended on the duration of diabetes (*P* for interaction <.001). For individuals with short diabetes duration (<5 years), the risk of death increased with poorer glycaemic control (increasing HbA1c), whereas for individuals with longstanding diabetes (≥5 years), we found a J-shaped association, where a mean HbA1c level between 6.5% and 7.9% [48 and 63 mmol/mol] was associated with the lowest risk of death. For individuals with longstanding diabetes, both low (<6.5% [<48 mmol/mol]; hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.07-1.37, *P* = .002) and high mean HbA1c levels (≥9.0% [≥75 mmol/mol]; HR 1.60, 95% CI 1.28-1.99, *P* < .001) were associated with an increased risk of death. We also calculated 5-year absolute risks of all-cause mortality, separately for short and long diabetes duration, and found similar risk patterns across different age groups, sex and comorbidity strata.

Conclusions: In elderly individuals with T2D, the effect of glycaemic control (measured by HbA1c) on all-cause mortality depended on the duration of diabetes. Of

particular clinical importance, we found that strict glycaemic control was associated with an increased risk of death among individuals with long (≥ 5 years) diabetes duration. Conversely, for individuals with short diabetes duration, strict glycaemic control was associated with the lowest risk of death. These results indicate that tight glycemic control may be beneficial in people with short duration of diabetes, whereas a less stringent target may be warranted with longer diabetes exposure.

KEYWORDS
death, elderly, hypoglycaemia, optimal glycaemic target, overtreatment, type 2 diabetes, variability

1 | INTRODUCTION

Up to one in four older adults (≥ 65 years) have type 2 diabetes (T2D),[1] and with the overall aging of the population, this number is likely to increase.[2] Compared with older individuals without diabetes, those with T2D are at increased risk of premature death,[3] functional disabilities,[4] hypertension,[5] coronary heart disease,[6] stroke,[6] and other geriatric comorbidities, including cognitive impairment,[7] depression,[8] falls,[9] polypharmacy[10] and hypoglycaemia.[11]

Despite the considerable burden of T2D in older adults, little is known about the specific risks and benefits associated with glycated haemoglobin (HbA1c) targets in older adults. This lack of evidence is partly attributable to the historical exclusion of older adults from clinical trials.[12] The UK Prospective Diabetes Study selectively excluded patients aged >65 years.[13] Although subsequent major clinical trials included individuals aged >65 years, the number of individuals aged >75 years at the time of enrolment was limited.[14-16] Moreover, there is a considerable heterogeneity in overall health status within the elderly, making it difficult to develop "one-size-fits-all" standards for the growing older community. Thus, clinical decision-making in older adults relies heavily on expert opinion and extrapolation of evidence from clinical trials of younger and healthier patients.[17]

Guidelines on diabetes care from multiple clinical organizations have all adopted the concepts of individualized glycaemic targets and care management by weighing treatment benefits against age, life expectancy, burden of comorbidity, functional and cognitive impairment. Although guidelines agree on individualization, they differ in the details of their recommendations, in terms of patient categories and glycaemic targets.[18-23]

Using a large contemporary primary care cohort of older adults with T2D, we aimed to investigate the effect of diabetes duration on glycaemic control and mortality risk, within different age, sex and clinically relevant comorbidity-defined subgroups.

2 | METHODS

2.1 | Study population

Until 2015, general practitioners working in the Copenhagen municipality and the former Copenhagen county referred their patients for blood sampling at one core facility (the Copenhagen General Practitioner's Laboratory; CGPL). From the CGPL, we identified all patients with T2D aged ≥65 years, who had three annual HbA1c measurements taken between 1 January 2005 and 31 December 2013. Individuals were included if they, in addition to the first HbA1c measurement, had two consecutive annual measurements of HbA1c, one after 1 year (±4 months) and another after 2 years (± 4 months). The baseline date for follow-up was set at the third measurement of HbA1c. For each individual, we defined our primary exposure as the mean HbA1c of the three measurements (Figure S1). A flowchart of study inclusion and exclusion criteria is provided in Figure S2. Individuals were categorized into clinically relevant mean HbA1c groups of <6.5% (<48 mmol/mol), 6.5%-6.9% (48 to 52 mmol/mol), 7%-7.9% (53 to 63 mmol/mol), 8%-8.9% (64 to 74 mmol/mol) and ≥9% (≥75 mmol/mol).

2.2 | HbA1c assays

Three commercially available assays were used to measure HbA1c in blood: the immunoassay Tina-quant Hemoglobin A1c II on a Roche Hitachi 911 Chemistry Analyser (Roche Diagnostics A/S, Hvidovre, Denmark); the immunoassay Advia 1650 (Bayer, Siemens, Healthcare Diagnostics, Tarrytown, New York); and the high-performance liquid chromatography-based assay Tosoh G7 and G8 (Tosoh Bioscience, Tokyo, Japan). All three assays were standardized according to the National Glycohaemoglobin Standardization Program (NGSP). The master equation NGSP = [0.09148 * International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)] + 2.152 was used to convert NGSP (% HbA1c) results to mmol HbA1c per mol HbA, as recommended by the IFCC. The Hitachi assay was used before December 2, 2002. The interserial coefficient of variation for the assay was 5.8% (at level 39 mmol/mol) and 5.2% (at level 78 mmol/mol), respectively. The correlation between the Hitachi and Advia assays was investigated by parallel analysis of 50 human blood samples during a period of 5 days in October 2002, and this confirmed the standardization of the assays. The Advia assay was used from 2 December 2002 until 25 January 2010 and the Tosoh assay after 25 January 2010 as described in detail by Borg et al.[24]

2.3 | Data sources

Citizens with a permanent address in Denmark are assigned a unique civil registration number, which allows linkage on an individual-level to nationwide administrative registries. The National Population Registry contains information on sex, date of birth, date of emigration and date of death.[25] The Danish National Patient Registry holds information on all hospitalizations, outpatient clinic and emergency room admissions.[26] When patients are discharged from the hospitals, contacts are registered with a primary discharge diagnosis, and subsequently classified according to the 10th revision of the International Classification of Disease (ICD-10). The Danish National Prescription Registry contains individual-level records on dispensing date, strength, quantity and drug type (using the Anatomical Therapeutic Chemical System), on all claimed drug prescriptions dispensed from pharmacies in Denmark.[27] Using these registries, we attained information on comorbidity, concomitant drug therapy, and outcomes. The cause of death, classified using ICD-10 codes, was extracted from the Danish Register of Causes of Death.[28] In accordance with Danish law, no approval from an ethics committee was needed in this registry-based study with no active participation from study subjects. The use of de-identified registry data was approved by the Danish Data Protection Agency (record number 2007-58-0015).

2.4 | Baseline variables and endpoints

Using the aforementioned nationwide administrative registries, we identified individuals with T2D, defined by a registry diagnosis of T2D and/or redeemed prescription of an oral antidiabetic drug or insulin. This definition has previously been shown to have a positive predictive value of 97%.[29] Individuals with a registry diagnosis of type 1 diabetes were excluded. For each individual, the following comorbidities were identified by discharge diagnoses prior to baseline: macrovascular disease, microvascular disease, atrial fibrillation, hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), depression, dementia, cancer without metastases, cancer with metastases, arthritis, urinary incontinence, falls, treatment with dialysis, alcohol-related contacts, as well as a registry diagnosis for obesity. Macrovascular disease was defined as a composite variable defined from discharge diagnoses of ischaemic stroke, myocardial infarction, peripheral vascular disease or from interventions, such as percutaneous coronary intervention, coronary artery bypass grafting or peripheral revascularization. Microvascular disease was defined as a composite variable based on discharge diagnoses of diabetic retinopathy or treatment with laser photocoagulation, mono- or polyneuropathy, end-stage renal disease or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2. To account for renal impairment, we used the last creatinine measurement obtained within 1 year prior to baseline. Creatinine was converted to eGFR, using the Modification of Diet in Renal Disease equation (eGFR [mL/min/1.73 m^2] = $175 \times [\text{creatinine}/88.4]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}]$).[30] Renal impairment was categorized as: stages 1 and 2: eGFR ≥ 60 mL/min/1.73 m^2; stage 3A: eGFR 45 to 59 mL/min/1.73 m^2; stage 3B: eGFR 30 to 44 mL/min/1.73 m^2; and stages 4 and 5: eGFR ≤29 mL/min/1.73 m^2. Fall traumas needing medical assistance was used as a proxy for frailty, and defined as discharge diagnoses of contusions or fractures of the head, upper or lower extremities within 5 years prior to baseline. Diabetes duration was categorized into levels of short (<5 years) and long (≥ 5 years) duration. Diagnoses and procedure codes are listed in Table S1. Use of pharmacotherapy was defined as one or more claimed prescribed drugs within 6 months prior to baseline. Individuals with multiple prescriptions (polypharmacy) were categorized into three groups (0-3, 4-5, ≥6 prescribed drugs). Treatment with the following drugs was assessed: antidiabetic medication; anti-hypertensive medications; antithrombotic medications; oral anticoagulant therapy; and statins. A detailed description of codes used to define concomitant pharmacological treatment is listed in Table S2. We defined hypertension as a registry diagnosis of hypertension or concomitant treatment with two or more types of anti-hypertensive drugs, as done previously.[31] The primary endpoint of interest was death from any cause. Secondary endpoints were death from cardiovascular disease and non-cardiovascular disease.

2.5 | Classification of comorbidity burden

In the most recent American Diabetes Association (ADA) and American Geriatric Society (AGS) guidelines, individual glycaemic targets are advised according to the number and severity of specific medical complexities listed in the guidelines.[18] By adopting the ADA/AGS guidelines, we constructed a modified ADA/AGS three-tier comorbidity classification.[18] Individuals were classified as "healthy", if they had at most two of the chronic comorbidities listed in Table S3, as having "moderate" comorbidity if they had three to five chronic comorbidities, and lastly, as having "severe" comorbidity, if they had at least six chronic comorbidities and/or had metastatic cancer disease, dementia and/or chronic kidney disease requiring dialysis, as described in the ADA/AGS guidelines.[18] We did not have data on staging with respect to heart failure and pulmonary disease, or data on functional status.

2.6 | Statistical analyses

Baseline characteristics of the study cohort were expressed as number (proportion), mean (SD) or median (interquartile range [IQR]), where appropriate. We used multiple Cox regression to study the effect of glycaemic control on the hazard of all-cause and cause-specific mortality. Three different models were used to calculate the hazard ratios (HRs). In model 1, we adjusted for baseline age group (65-70 years, 70-75 years and >75 years) and sex. In model 2, we additionally adjusted for prevalent comorbidity (macrovascular disease, microvascular disease, atrial fibrillation, hypertension, congestive heart failure, COPD, depression, dementia, arthritis, urinary incontinence, falls, treatment with dialysis, cancer with and without metastases, alcohol-related diagnoses and obesity) and calendar year at baseline (third measurement), to account for changes in healthcare delivery over time. Model 3 represented the fully adjusted model, where we additionally adjusted for concomitant medication (antithrombotic medication, anticoagulant therapy, lipid-lowering medication, antidiabetic medication). Use of

antidiabetic medication was analysed as independent variables: metformin, sulphonylureas and insulin (treatment vs. no treatment). Treatment with α-glucosidase inhibitors, thiazolidinediones and newer drug classes, such as incretin drugs and selective glucose reuptake inhibitors, were categorized as one group, as the drug exposure for these drugs was negligible during the study period (Table S2). The mean HbA1c category with the lowest hazard was selected as reference. Time zero for all time-to-event analyses was the date of third HbA1c measurement (baseline). Individual follow-up ended in case of death, emigration from Denmark, or at 31 December 2015, whichever occurred first. We also constructed a risk chart, displaying the 5-year absolute risks of all-cause mortality for different combinations of age groups, sex and medical complexities, by mean HbA1c categories. Risk charts were separately reported for short and long diabetes duration and predicted using Cox regression.

2.7 | Sensitivity analyses

To test the robustness of our results, we conducted a number of sensitivity analyses. First, to evaluate the functional relationship between mean HbA1c and diabetes duration, we constructed a two-dimensional contour plot, based on restricted cubic splines using Cox regression. We modelled an interaction term between mean HbA1c and diabetes duration, considering both as continuous variables instead of categories. Knots were set at the 5th, 50th and 95th percentiles. Second, to test whether any association was dependent on the number of measurements, we conducted additional analyses using one or two (±4 months) annual measurements only, respectively. Third, to test whether a more strict or liberal time-related inclusion yielded similar results, we included individuals with three HbA1c measurements, annually spaced ±3 and ± 5 months, respectively. Fourth, as an alternate measure for glycaemic control, we tested whether the use of the last HbA1c (third measurement) instead of the mean HbA1c yielded comparable results. Fifth, to further explore whether any association with mortality could be confounded by hypoglycaemia, we adjusted the main model for hypoglycaemic events prior to baseline. Last, recent evidence suggests that variability, that is, glycaemic fluctuations over time, provides additional prognostic information, independent of glycaemic control, with regard to mortality in patients with T2D.[32,33] To address the effect of variability on the association between mean HbA1c and mortality risk, we adjusted the main models for HbA1c variability. Variability was defined as the standard deviation of the residuals, obtained using linear regression on the three measurements, as has been done previously (Figure S1).[31] Variability was categorized into tertiles (low, moderate and high variability). We also accounted for the overall trend in HbA1c by adjusting for the slope (beta) estimate, which was also categorized into tertiles (decreasing, stable and increasing trend).

Potential effect modifications between mean HbA1c levels and outcome hazard rates by age groups, sex, diabetes duration and comorbidity burden, were evaluated using likelihood ratio tests comparing the main model to a model containing the interaction term. A two-sided *P* value <.05 was taken to indicate statistical significance. The R statistical program (R Foundation, version 3.3.3, available at http://www.r-project.org) and R libraries: survival, rms (version 5.3), riskRegression (version 29 January 2019), Publish (version 6 April 2018), forestplot (version 1.9), ggplot2 (version 2.2.1) were used for all statistical analyses and graphical presentations.

3 | RESULTS

3.1 | Baseline demographics and clinical characteristics

We identified 9734 individuals with T2D aged ≥65 years, who had three successive annual HbA1c measurements. The baseline clinical characteristics of the study population, grouped by diabetes duration, are provided in Table 1. The median (IQR) age of the population at baseline was 73.5 (69.0-79.3) years, with a similar proportion of women and men. Just over half of the individuals (52.0%) had a mean HbA1c level 6.5% (<48 mmol/mol). Individuals with longstanding diabetes had higher levels of HbA1c, were older, were more often prescribed sulphonylureas and insulin and had more severe comorbidity, such as late diabetic complications and cardiovascular disease.

3.2 | Short diabetes duration (<5 years), glycaemic control and risk of all-cause mortality

During a median (IQR) follow-up time of 7.3 (4.6-8.7) years, 3320 individuals died. We found that the association between mean HbA1c and the hazard of all-cause mortality depended on the duration of diabetes (*P* for interaction <.001). In the short diabetes duration group, 1578 deaths occurred during follow-up, of which 405 were deaths from cardiovascular causes, and 1173 were deaths from non-cardiovascular causes, respectively. For individuals with short diabetes duration, the hazard of all-cause mortality increased in a stepwise manner, with the lowest hazard associated with mean HbA1c <6.5% (<48 mmol/mol; Figure 1A, model 1). The point estimates were slightly attenuated, when we adjusted for disease- and age-related comorbidity and concomitant medication. However, we observed a similar dose-response relationship, with the highest hazard for all-cause mortality associated with mean HbA1c levels of 8.0%-8.9% (64 to 74 mmol/mol; HR 1.50, 95% CI 1.18-1.90, *P* < .001[Figure 1A, model 3]). We also calculated 5-year absolute risks of all-cause mortality (Figure 2), and found that the risk of all-cause mortality increased with increasing levels of HbA1c, irrespective of age, sex and comorbidity strata. When evaluating the relationship between levels of glycaemia and diabetes duration as continuous variables, we found that the hazard of death increased with increasing levels of glycaemia for individuals with shorter diabetes duration (Figure 3). A similar pattern of association with overall higher point estimates was observed for non-cardiovascular deaths. For cardiovascular deaths, the direction of effect was similar to the main model, albeit with none of the associations reaching statistical significance (Figure 4). We found no effect modification with respect to age, sex or comorbidity (*P* for interaction >.05).

TABLE 1 Baseline characteristics of the study cohort

Characteristics	Total population n = 9734	Diabetes duration		P
		Short duration (<5 y) n = 6072	Long duration (≥5 y) n = 3662	
HbA1c category, n (%)				
6.5% (<48 mmol/mol)	5064 (52.0)	3751 (61.8)	1313 (35.9)	<.001
6.5%-6.9% (48-52 mmol/mol)	1961 (20.1)	1173 (19.3)	788 (21.5)	
7.0%-7.9% (53-63 mmol/mol)	1856 (19.1)	843 (13.9)	1013 (27.7)	
8.0%-8.9% (64-74 mmol/mol)	575 (5.9)	212 (3.5)	363 (9.9)	
9% (≥75 mmol/mol)	278 (2.9)	93 (1.5)	185 (5.1)	
Median (IQR) diabetes duration, y	3.2 (2.2-7.7)	2.3 (2.1-3.0)	9.3 (6.9-11.9)	<.001
Calendar period (tertiles), y				
Q1 (2006-2007)	4288 (44.1)	1719 (28.3)	2569 (70.2)	<.001
Q2 (2008-2010)	2771 (28.5)	1938 (31.9)	833 (22.7)	
Q3 (2011-2013)	2675 (27.5)	2415 (39.8)	260 (7.1)	
Demographics				
Median (IQR) age, y	73.5 (69.0-79.3)	72.9 (68.6-78.4)	74.7 (69.7-80.6)	<.001
Male, n (%)	4874 (50.1)	3024 (49.8)	1850 (50.5)	.507
Medication				
Glucose-lowering drugs, n (%)				
Insulin	520 (5.3)	82 (1.4)	438 (12.0)	<.001
Metformin	3585 (36.8)	2548 (42.0)	1037 (28.3)	<.001
Sulphonylureas	1453 (14.9)	793 (13.1)	660 (18.0)	<.001
Other OAD	311 (3.2)	167 (2.8)	144 (3.9)	.002
Number of glucose lowering drugs, n (%)				
0	4438 (45.6)	2721 (44.8)	1717 (46.9)	
1	4744 (48.7)	3115 (51.3)	1629 (44.5)	
2	532 (5.5)	233 (3.8)	299 (8.2)	
≥3	20 (0.2)	3 (0.1)	17 (0.4)	
Anti-hypertensive drugs, n (%)				
RAS inhibitors	1944 (20.0)	1207 (19.9)	737 (20.1)	.787
Beta blockers	1747 (17.9)	1138 (18.7)	609 (16.6)	.009
Calcium antagonists	902 (9.3)	565 (9.3)	337 (9.2)	.894
Loop diuretics	542 (5.6)	309 (5.1)	233 (6.4)	.009
Aldosterone antagonists	340 (3.5)	193 (3.2)	147 (4.0)	.034
Other drugs, n (%)				
Oral anticoagulants	686 (7.0)	444 (7.3)	242 (6.6)	.203
Antithrombotic drugs	1826 (18.8)	1038 (17.1)	788 (21.5)	<.001
Statin	2818 (29.0)	1759 (29.0)	1059 (28.9)	.976
Polypharmacy, number of drugs, n (%)				
0-3	8905 (91.5)	5613 (92.4)	3292 (89.9)	<.001
4-5	816 (8.4)	451 (7.4)	365 (10.0)	
≥6	13 (0.1)	8 (0.1)	5 (0.1)	
Medical history				
Chronic kidney disease, n (%)				
eGFR category ≤2 (≥ 60 mL/min/1.73 m^2)	7090 (72.8)	4748 (78.2)	2342 (64.0)	<.001
eGFR category 3a (45-59 mL/min/1.73 m^2)	1897 (19.5)	984 (16.2)	913 (24.9)	
eGFR category 3b (30-44 mL/min/1.73 m^2)	630 (6.5)	297 (4.9)	333 (9.1)	
eGFR category ≥4 (≤ 29 mL/min/1.73 m^2)	117 (1.2)	43 (0.7)	74 (2.0)	

(Continues)

TABLE 1 (Continued)

Characteristics	Total population n = 9734	Diabetes duration		P
		Short duration (<5 y) n = 6072	Long duration (≥5 y) n = 3662	
Hypoglycaemia, n (%)	187 (1.9)	36 (0.6)	151 (4.1)	<.001
Myocardial infarction, n (%)	1390 (14.3)	795 (13.1)	595 (16.2)	<.001
Stroke, n (%)	1387 (14.2)	751 (12.4)	636 (17.4)	<.001
Peripheral artery disease, n (%)	536 (5.5)	275 (4.5)	261 (7.1)	<.001
Diabetic neuropathy, n (%)	705 (7.2)	197 (3.2)	508 (13.9)	<.001
Diabetic retinopathy, n (%)	712 (7.3)	202 (3.3)	510 (13.9)	<.001
Diabetic nephropathy, n (%)	308 (3.2)	95 (1.6)	213 (5.8)	<.001
Dialysis, n (%)	<4 (<0.0)	<4 (<0.0)	<4 (<0.0)	.996
Congestive heart failure, n (%)	1144 (11.8)	631 (10.4)	513 (14.0)	<.001
Atrial fibrillation, n (%)	1283 (13.2)	778 (12.8)	505 (13.8)	.177
Hypertension, n (%)	7406 (76.1)	4565 (75.2)	2841 (77.6)	.008
COPD, n (%)	899 (9.2)	581 (9.6)	318 (8.7)	.154
Dementia, n (%)	152 (1.6)	69 (1.1)	83 (2.3)	<.001
Depression, n (%)	101 (1.0)	58 (1.0)	43 (1.2)	.352
Arthritis, n (%)	261 (2.7)	163 (2.7)	98 (2.7)	1.00
Falls, n (%)	1053 (10.8)	596 (9.8)	457 (12.5)	<.001
Urinary incontinence, n (%)	258 (2.7)	159 (2.6)	99 (2.7)	.851
Cancer, n (%)	1521 (15.6)	1001 (16.5)	520 (14.2)	.003
Metastatic cancer, n (%)	111 (1.1)	80 (1.3)	31 (0.8)	.043
Alcohol-related contacts, n (%)	172 (1.8)	98 (1.6)	74 (2.0)	.163
Obesity registry diagnosis, n (%)	876 (9.0)	501 (8.3)	375 (10.2)	.001
AGS/ADA medical complexity status, n (%)				
Healthy	7017 (72.1)	4560 (75.1)	2457 (67.1)	
Moderate comorbidities	2372 (24.4)	1325 (21.8)	1047 (28.6)	
Severe comorbidities	345 (3.5)	187 (3.1)	158 (4.3)	<.001

Note: Due to Danish data protection regulation (the Act on Processing of Personal Data), any observations <4 may not be reported. Diagnoses of obesity and alcohol were obtained from registry diagnoses.

Abbreviations: ADA, American Diabetes Association; AGS, American Geriatric Society; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; n, number of individuals; OAD, oral antidiabetic drug; RAS, renin-angiotensin system.

3.3 | Long diabetes duration (≥5 years), glycaemic control and risk of all-cause mortality

For individuals with longstanding diabetes, 1742 individuals died during follow-up, of whom 478 died from cardiovascular causes and 1264 died from non-cardiovascular causes. We found a J-shaped association between mean HbA1c categories and all-cause mortality across all three models (Figure 1B). We found that both the lowest (mean HbA1c <6.5% [< 48 mmol/mol]; HR 1.21, 95% CI 1.07-1.37, P = .002 [Figure 1B, model 3]) and the highest (mean HbA1c 9.0% [≥ 75 mmol/mol]; HR 1.60, 95% CI 1.28-1.99, P < .001[Figure 1B, model 3]) HbA1c categories were significantly associated with an increased hazard of all-cause mortality. The mean HbA1c category with the lowest hazard of all-cause mortality was 6.5%-7.9% (48 to 63 mmol/mol). For non-cardiovascular mortality, the pattern of association was similar to that for all-cause mortality. We found no significant association with cardiovascular death (Figure 4), albeit the point estimates tracked in the same direction. The lowest 5-year absolute risk of death was also associated with mean HbA1c levels between 6.5%-7.9% (48 and 63 mmol/mol), irrespective of the degree of comorbidity or sex and age group, with increased risks at both low and high levels of glycaemia (Figure 2). With increasing duration of diabetes, the hazard of all-cause mortality shifted from a linear, towards a non-linear pattern, with the highest hazard among individuals very long diabetes duration and low levels of glycaemia (Figure 3). We found no effect modification with respect to age, sex or comorbidity (P for interaction >.05).

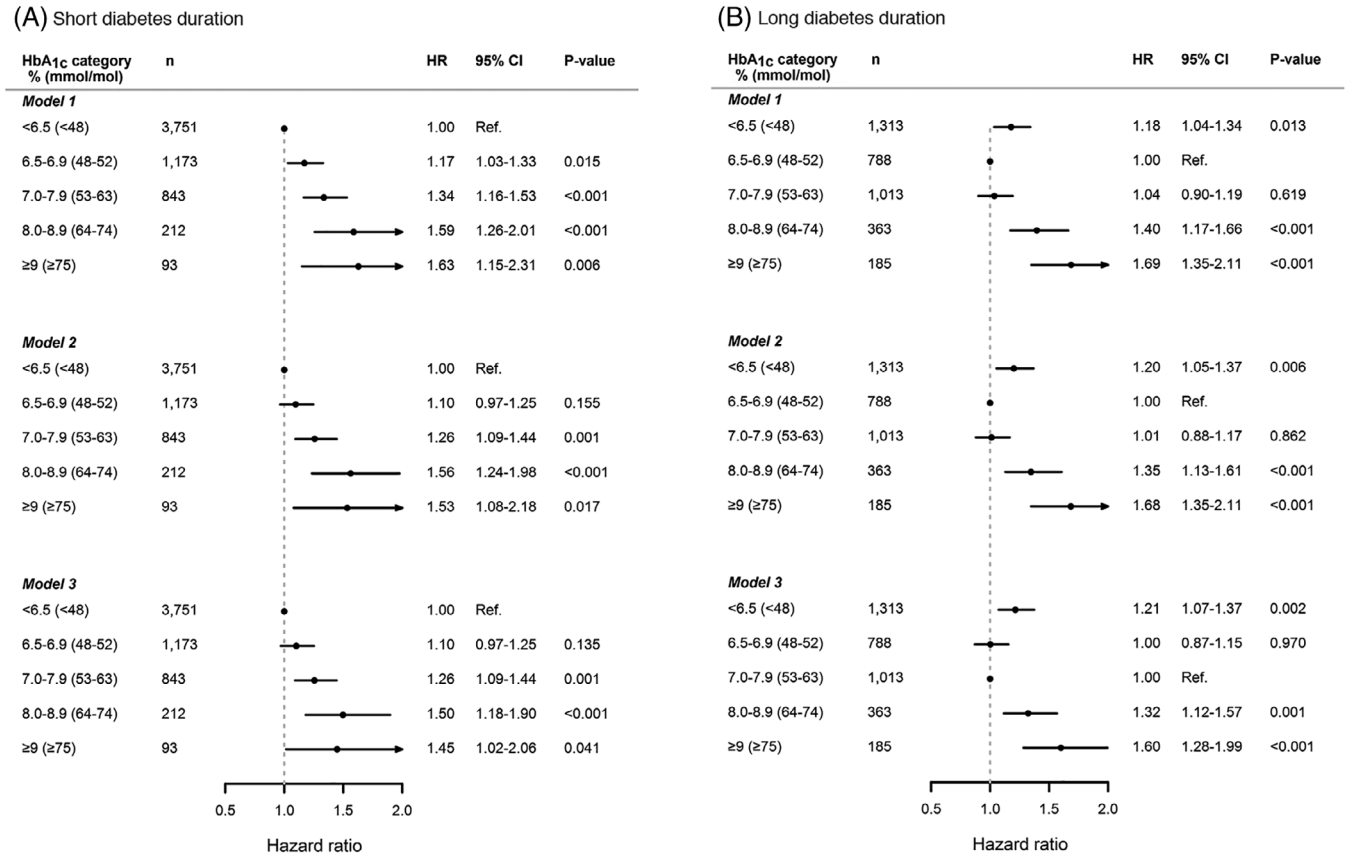

FIGURE 1 Glycated haemoglobin (HbA1c) categories and the hazard ratio (HR) of all-cause mortality by groups of A, short (<5 years) and B, long (≥5 years) diabetes duration. Model 1 was adjusted for age groups (65-70 years, 70-75 years and > 75 years) and sex. Model 2 was additionally adjusted for comorbidity (macrovascular disease, microvascular disease, atrial fibrillation, hypertension, congestive heart failure, chronic obstructive pulmonary disease, depression, dementia, cancer, arthritis, urinary incontinence, falls, treatment with dialysis, cancer with metastases, alcohol-related diagnoses, and obesity) and calendar period. Model 3 represented the fully adjusted model, where we additionally adjusted for concomitant medication (antithrombotic medication, anticoagulant therapy, lipid-lowering medication, and antidiabetic medication). The solid dots refer to the HR's, and horizontal lines represent 95% confidence intervals (CI). The HbA1c category with the lowest hazard was selected as reference

3.4 | Glycaemic control by degree of comorbidity

To evaluate glycaemic control levels among older adults with T2D by overall health status, we categorized individuals based on the number and severity of comorbidities (Table S4). Overall, we found that 70.7% and 69.5% of patients with moderate and severe comorbidity, respectively, had glycaemic levels 7% (<53 mmol/mol). We also found that individuals with moderate and severe comorbidity were generally older, had longer diabetes duration, and were more often treated with multiple drugs, in particular sulphonylureas and insulin, compared with individuals classified as healthy (Table S4). Of those treated with glucose-lowering drugs, 19.1% and 30.9% of the individuals classified as having severe comorbidity, were treated with insulin and sulphonylureas, respectively. The proportion of individuals with moderate comorbidity receiving insulin corresponded to 12.9% and 30.4% for sulphonylureas. Of individuals classified as healthy, 8.4% received insulin and 26.3% a sulphonylurea, respectively.

3.5 | Sensitivity analyses

To test the robustness and generalizability of our associations, we conducted seven sensitivity analyses. The results did not materially change when modelling the exposure as a continuous variable (Figure 3). Nor did the pattern of association change when using a different number of measurements, different time-related cut-offs for inclusion, an alternate exposure of HbA1c (last measurement instead of mean HbA1c) or adjusting the main model for hypoglycaemic events, HbA1c variability or trend (Figure S3). Moreover, we found that the hazard of death increased monotonically with increasing HbA1c variability for individuals with short duration of diabetes, but not for individuals with longstanding diabetes. Also, increasing trend compared with a stable trend in HbA1c was associated with increased hazard of death in both individuals with short and long duration of diabetes. However, a decreasing trend was only associated with increased hazard in individuals with longstanding disease.

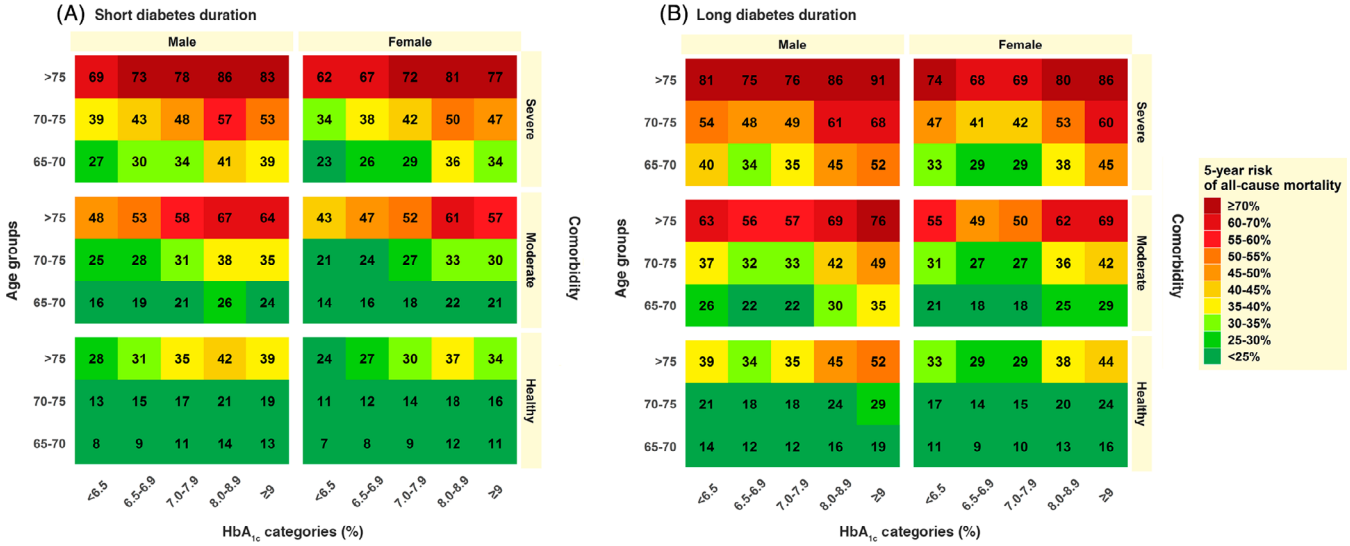

FIGURE 2 Five-year absolute risk prediction chart for all-cause mortality, based on individuals with A, short (<5 years) and B, long (≥5 years) diabetes duration, and the combination of age groups, sex and comorbidity, with respect to different levels of mean glycated haemoglobin (HbA1c, in %). Individuals were classified as healthy, if they had ≤2 comorbidities, moderate if they had three to five comorbidities, and severe, if they had ≥6 comorbidities and/or had metastatic cancer disease, dementia, or chronic kidney disease requiring dialysis. The colour scheme refers to the absolute 5-year risk (%) for all-cause mortality

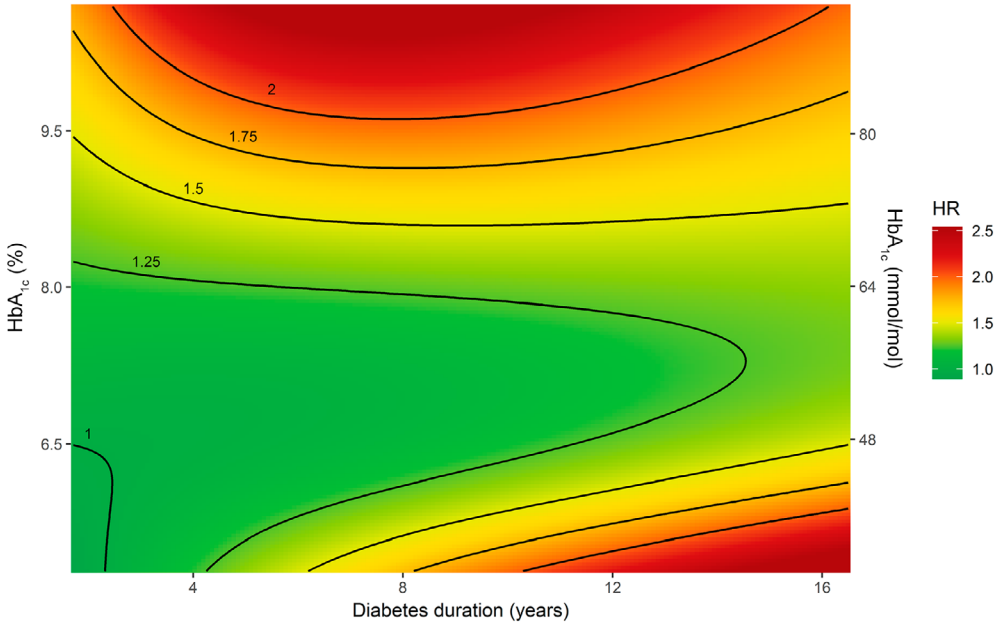

FIGURE 3 Contour plot displaying the functional relationship between levels of mean glycated haemoglobin (HbA1c; mmol/mol and %) and diabetes duration (years), using restricted cubic splines regression. Knots were set at the fifth, 50th and 95th percentile. A mean HbA1c value of 6.5% (48 mmol/mol) and diabetes duration of 2 years was set as reference. Only data between the 10th and 90th percentile is shown, to avoid presenting results for mean HbA1c and diabetes duration values for which the number of observations were small. The solid lines and the colour scheme refer to the hazard ratio (HR) for all-cause mortality. The model was adjusted as described in Figure 1 (model 3)

4 | DISCUSSION

Using real-world data of older primary care patients with T2D, we found that the association between glycaemic control and the risk of death depended on the duration of diabetes. For individuals with short diabetes duration (<5 years), we found that the risk of death increased with poorer glycaemic control, whereas for individuals with longstanding diabetes (≥5 years), we found a J-shaped association,

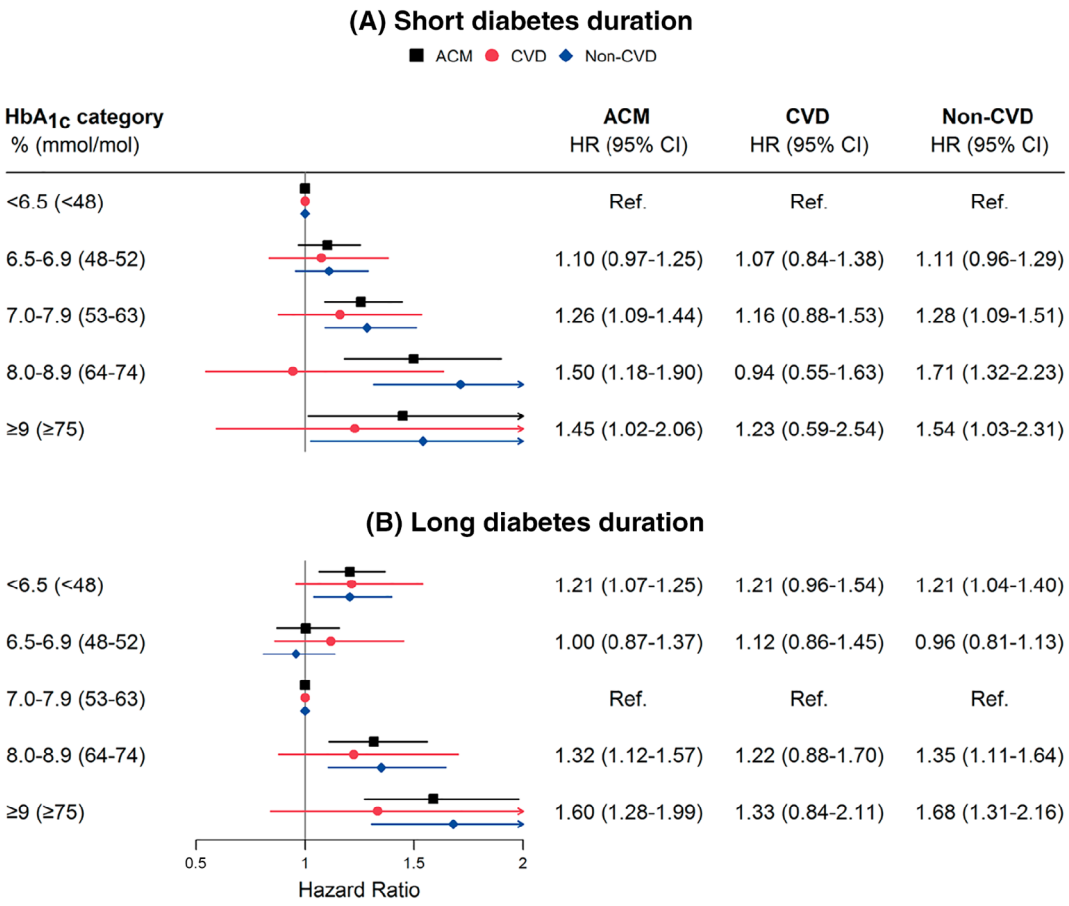

FIGURE 4 Glycated haemoglobin (HbA1c) categories and the hazard rate of cardiovascular (CVD, red) and non-cardiovascular (non-CVD, blue) mortality by groups of A, short (<5 years) and B, long (≥ 5 years) diabetes duration. Results from the main model (Figure 1, model 3, black) is shown for comparison. The model was adjusted as described in Figure 1 (model 3). The solid markers refer to the hazard ratios (HR), and horizontal lines represent the 95% confidence intervals (CI). ACM, all-cause mortality

with the lowest risk associated with glycaemic levels between 6.5%-7.9% (48 and 63 mmol/mol). These results were consistent across different age, sex and comorbidity-defined subgroups.

Previous studies on middle-aged patients with T2D have shown conflicting results concerning the relationship between glycaemic control, diabetes duration and mortality risk. For instance, in a recent study by Laiteerapong et al.[34] the authors found that newly diagnosed middle-aged patients with tight glycaemic control (6.5% [<48 mmol/mol]) had the lowest mortality risk, with increasing effect sizes with longer exposure to poor glycaemic control.[34] As opposed to our results on elderly patients, they found no increased mortality risk in the normoglycaemic range with increasing duration of diabetes. In another, smaller study (531 individuals) of middle-aged patients with T2D, it was found that long diabetes duration (≥5 years) and good glycaemic control (<6.5% [48 mmol/mol]) was associated with increased risk of death. However, no incremental risk was observed in patients with a combination of longstanding diabetes and higher levels of glycaemia.[35] Lastly, a duration-dependent relationship has also been reported for cardiovascular events in a post hoc analysis of the Veterans Affairs Diabetes Trial, where patients in the intensive arm, who entered the trial with a diabetes duration >15 years, had a higher risk of macrovascular events, compared with the standard arm.[31] We are, to the best of our knowledge, the first to extend this duration-dependent relationship between glycaemic control and mortality risk to an elderly population with T2D. We are also the first to report that significant risk exists in both the higher and lower tails of glycaemia in elderly patients with longer diabetes exposure.

The interaction between diabetes duration and glycaemic control on the risk of death that we report could potentially also explain the inconsistencies between previous observational studies on older patients with T2D, which have reported both linear[32,33] and non-linear relationships[30,34,35] between levels of glycaemia and mortality risk. Although the present study does not allow for causal inference due to its observational design, our results suggest that aiming for normoglycaemic levels in those with short duration of diabetes may be beneficial, whereas for individuals with long diabetes duration, setting universal goals may be less straightforward. In these patients, additional important factors, such as frailty, life expectancy and patient preferences should be considered, to better provide patient-centred care that balances the pros and cons of tight glycaemic control.

Several factors may explain the observed mortality risk associated with long diabetes duration and HbA1c levels in the lower region. Hypoglycaemia is a potent candidate mechanism. We found that individuals with longstanding diabetes were more often prescribed sulphonylureas and insulin compared with individuals with short diabetes duration (Table 1 and Tables S5 and S6). These drugs can by themselves, or in concert with malnourishment, severe comorbidity, cognitive impairment and/or polypharmacy, induce hypoglycaemia, all of which were more prevalent in the long diabetes duration group. Hypoglycaemia, in particular in the elderly, is important to prevent, as it is associated with falls, cognitive impairment, hospitalizations, cardiovascular events and mortality risk.[18,36-38] Also, low levels of glycaemia may not always be indicative of intentional good glycaemic control, but rather a proxy for poor nutritional status and general frailty, both of which have been associated with increased mortality risk.[39] The latter is supported by the existence of a J-shaped association between levels of glycaemia and mortality risk in non-diabetic populations, suggesting that non-glycaemic factors may partly explain the observed risk in the lower glycaemic range.[40]

In terms of glycaemic variability, our results are in accordance with previous studies that have shown that higher variability in HbA1c is associated with an increased risk of mortality in patients with T2D.[33,41] However, the present study provides additional evidence that, at least in older adults, the prognostic effect of HbA1c variability may be specific to patients with short duration of diabetes, but not long duration. By contrast, a decreasing trend in HbA1c in the present study was associated with increased risk of death in patients with long diabetes duration, but not in those with short duration. From a clinical standpoint, variability might represent an important prognostic marker in patients with short duration of diabetes, whereas physicians may need to be more attentive not only to low levels of glycaemia, but also unintentional decreasing HbA1c over time, in particular in patients with longstanding diabetes.

In the present study, we also found signs of potential overtreatment of older adults with T2D. Almost 70% of individuals with moderate and severe comorbidity had tight glycaemic control (<7.0% [<53 mmol/mol]) and, concurrently, the largest proportion of risk factors for severe hypoglycaemia (eg, older age, polypharmacy, severe renal impairment) compared with the healthy group (Table S4). Nearly 50% of the individuals across all three tiers did not receive any glucose-lowering drugs; however, among those who did, individuals with moderate and severe comorbidity were more often prescribed regimens containing insulin and sulphonylureas, compared with the healthy group. These data indicate that guideline recommendations may not have been fully adopted into clinical practice in Denmark, and that a substantial proportion of patients that are traditionally considered at high risk of hypoglycaemia and other adverse effects, do not receive appropriate de-intensification of their treatment, despite the fact that existing recommendations in geriatric diabetes advocate a more moderate practice in this patient group. These data complement previous concerns about the frequency of overtreatment in older adults with T2D.[42-44]

We found no evidence of differences in optimal treatment targets across the three comorbidity tiers. However, this does not invalidate differentiated treatment goals by different comorbidity strata, as advised by current clinical recommendations. For healthy older people, with short diabetes duration and extended life expectancy, a glycaemic target similar to that for younger patients (7% [<53 mmol/mol]) may be appropriate. In accordance with our data, tight glycaemic control may also be appropriate in patients with several comorbidities (Figure 2), as long as it is in line with the patient's preferences and achieved through low risk intervention, for example, lifestyle modification and/or metformin. However, in patients with very long diabetes duration, limited life expectancy, cognitive impairment and/or functional dependencies, a conservative treatment target is warranted, as treatment benefits are most likely outweighed by the risk of harm. At present, only the Department of Veterans Affairs[22] advocates differentiated treatment of older adults based on levels of comorbidity and diabetes duration. Based on our results, we suggest that other major clinical recommendations should in addition to individual medical complexity, also consider diabetes duration as an important discerning factor, when setting individual goals for older patients with T2D.

The strengths of the present study include a large population-based primary care sample of elderly patients with T2D, long-term follow-up, and utilization of clinical and administrative registries, taking multiple disease- and age-related comorbidities into account. Moreover, we used serial HbA1c, allowing a more detailed evaluation of long-term glycaemic control, as well as being able to account for the effect of temporal fluctuations in HbA1c.

Some limitations of this study should also be noted. We did not have information on functional limitations, for example, activities of daily living; however, our data were collected from available laboratory records as part of the patient's routine clinical follow-up, suggesting that our results are most likely based on patients with a certain degree of self-management and preserved functional abilities. We did not have information on the indication for HbA1c testing; thus, patients with three annual measurements could, in theory, represent a selected group of patients. We found that individuals with non-annual measurements were slightly older, with longer duration of diabetes, had marginally poorer glycaemic control, more diabetes-related late complications and other major comorbidities (Table S7). However, we do not believe that this selection of patients has affected the generalizability of our results, as we found similar results for individuals with one, two and three annual measurements, as well as for individuals with a non-annual referral pattern.

In conclusion, this cohort study of older primary care patients aged ≥65 years with T2D demonstrates that the risk of mortality differs by levels of glycaemia and duration of the disease. For individuals with short diabetes duration (<5 years), we found that the risk of death increased with poorer glycaemic control, whereas for individuals with longstanding diabetes (≥5 years), we found a J-shaped association, with the lowest risk associated with glycaemic levels of 6.5%-7.9% (48 to 63 mmol/mol).

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CONFLICT OF INTERESTS

J.G., J.L.I., M.W.S., J.K.K, B.L., M.S.O. and J.B.N. have no conflict of interest to disclose. A.G.H. is an employee of Novo Nordisk A/S, Denmark. J.H.S. has received research grants from Medtronic, Biotronik and Gilead, personal fees as speaker for Medtronic, Biotronik, AstraZeneca and Boehringer Ingelheim and personal fees as a member of an advisory committee in Medtronic.

AUTHOR CONTRIBUTIONS

J.G., J.L.I, J.K.K, M.W.S, A.G.H. and J.B.N. made primary contributions to study conception, design, statistical analyses, interpretation of results, and writing of the manuscript. B.L. collected the HbA1c data and described the HbA1c assays. All authors contributed to interpretation of results, all revised the manuscript critically for important intellectual content, and all approved the final manuscript. J.B.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA-SHARING

Due to Danish data protection legislation, raw data and study materials will not be made available to other researchers.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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